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Differential expression of interferon alpha inducible genes in peripheral blood mononuclear cells from patients chronically infected with hepatitis C virus and healthy donors

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ABSTRACT

The impact of exposure to interferon-alpha (IFN-α) on gene expression in peripheral blood mononuclear cells (PBMC) from hepatitis C virus (HCV)-infected and healthy individuals was investigated to recognize whether their PBMC differ in expression of IFN-inducible genes (ISGs) following treatment with IFN-α2b. PBMC obtained from healthy and treatment-naïve HCV-infected patients were cultured with IFN-α2b for 30 min, 2 h, 4 h and 72 h, and gene expression was analyzed using mRNA microarray technology. IFN-α caused differential up-regulation of many known ISGs in PBMC from both HCV-infected and healthy subjects. In comparison to untreated controls, the highest augmentation in PBMC ISG expression occurred after 4-hour exposure to IFN-α2b in both groups. The analysis identified 84 transcripts, representing 64 known and 2 unknown genes, that were up-regulated by at least 5-fold in PBMC from infected and uninfected individuals. However, the expression of IFN-α inducible genes was impaired in the PBMC from HCV-infected individuals compared to healthy controls. This was due to an increased baseline expression of the transcripts in PBMC of HCV-infected patients. These findings expand our understanding of IFN-responses in HCV-infected individuals and suggest that functions of PBMC, which include immune effector cells, are altered in patients chronically infected with HCV.

1. Introduction

Hepatitis C virus (HCV) is a single-stranded RNA virus that affects an estimated 150 million people worldwide as a symptomatic chronic infection. The virus establishes clinically evident chronic hepatitis in the majority of those infected [1]. It can also initiate persistent asymptomatic (occult) infection identified using virus detection techniques of a greater sensitivity than those conventionally used in clinical laboratories [2–4]. Prior to the advent of direct acting antivirals (DAA) for the treatment of chronic hepatitis C (CHC), the standard therapy included intravenously administered pegylated interferon (PegIFN)-α2a (180 μg/week) or PegIFN-α2b (1.5 μg/kg week) in combination with ribavirin (PegIFN/RBV) administered orally at doses of 0.8 to 1.2 g/day depending on body weight [5,6]. PegIFN/RBV therapy alone or in combination with DAA remains widely used and may remain utilized for specific groups of adults and pediatric patients, and in regions where DAA might be not readily accessible.

The mechanism by which IFN-α suppresses HCV replication in the chronically infected host is not clear. However, it has been shown that cell-specific induction of IFN-α-stimulated genes (ISGs), depending on the cell type, may be positively or negatively associated with responses to anti-HCV therapy [7]. As well, it has been found that early treatment with IFN-α is more effective at eliciting a clinically apparent sustained virological response (SVR) than therapy later in the course of infection [8]. Although considered to be primarily hepatotropic, experimental and clinical data demonstrate that the virus is capable of invading and replicating in extrahepatic cells, including those of the immune system [9–14].

In the current study, the impact of ex vivo exposure to recombinant IFN-α2b on the gene expression profiles in peripheral blood mononuclear cells (PBMC) from HCV-infected and uninfected individuals was investigated using Affymetrix mRNA microarray technology. The data published are limited in regard to this issue. However, several studies have examined differences in PBMC and liver gene expression signatures in HCV-infected individuals who respond or do not respond to IFN therapy [15–18]. In one relevant study, expression of ISGs was

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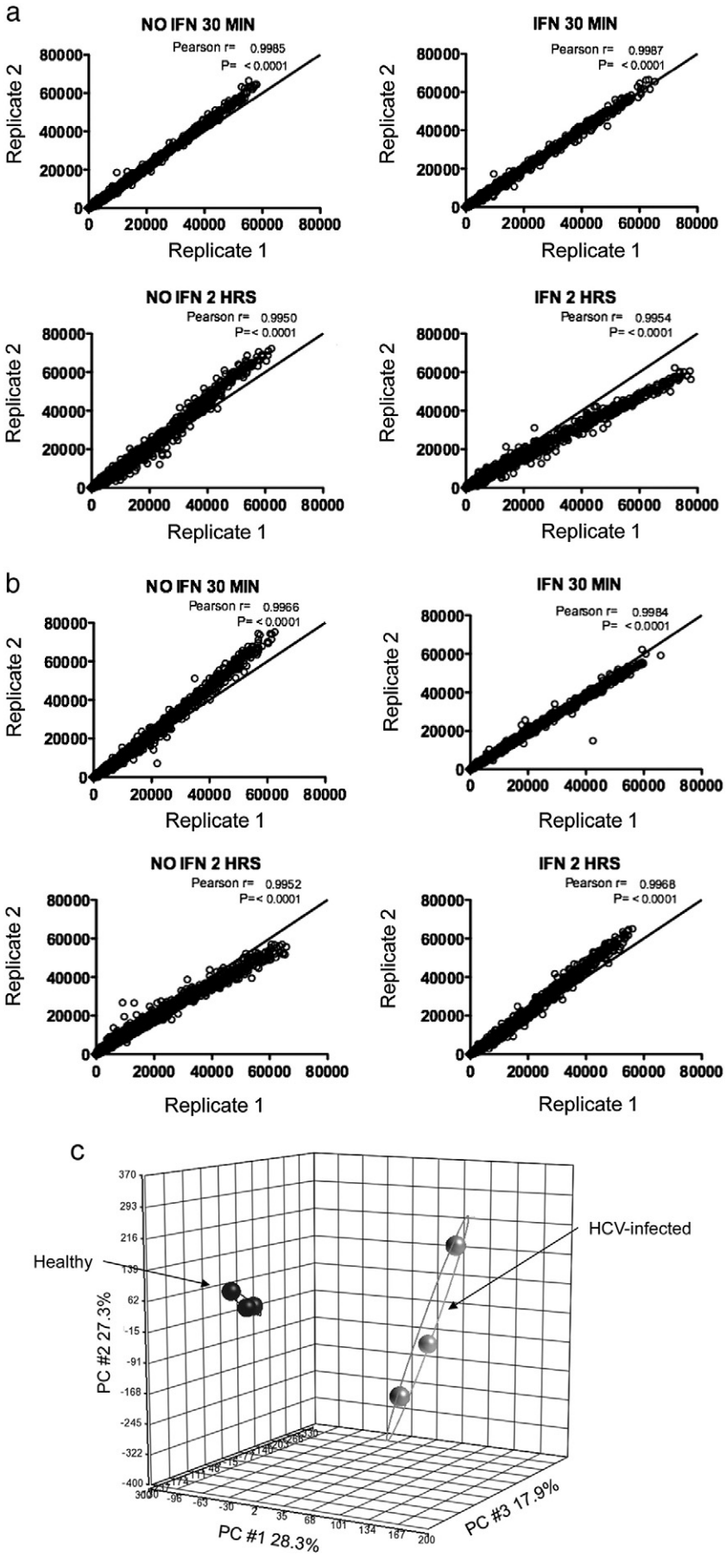
a
NO IFN 30 MIN
Pearson r= 0.9985
P= < 0.0001
IFN 30 MIN
Pearson r= 0.9987
P= < 0.0001
NO IFN 2 HRS
Pearson r= 0.9950
P=< 0.0001
IFN 2 HRS
Pearson r= 0.9954
P= < 0.0001
b
NO IFN 30 MIN
Pearson r= 0.9966
P= < 0.0001
IFN 30 MIN
Pearson r= 0.9984
P= < 0.0001
NO IFN 2 HRS
Pearson r= 0.9952
P=< 0.0001
IFN 2 HRS
Pearson r= 0.9968
P= < 0.0001
Replicate 1
Replicate 2
0
20000
40000
60000
80000
c
Healthy
HCV-infected
PC #1 28.3%
PC #2 27.3%
PC #3 17.9%